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     PROMT, AQUASCI, CEABA-VTB, DRUGU, ...' ENTERED AT 12:19:32 ON 02 JUL 2002
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L4           462 S L3 AND (ADMINIST? OR THERAPEUT? OR DOSE)
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L6           130 DUP REM L5 (4 DUPLICATES REMOVED)
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L10            0 S 6080383

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L1: Entry 1 of 1 File: USPT Jun 27, 2000

US-PAT-NO: 6080383
DOCUMENT-IDENTIFIER: US 6080383 A

TITLE: Method and composition for the treatment of cancer by the enzymatic conversion of soluble radioactive toxic agents into radioactive toxic precipitates in the cancer

DATE-ISSUED: June 27, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rose; Samuel	Oakland	CA	94608	

US-CL-CURRENT: 424/1.69; 424/1.11, 424/1.57, 424/9.1, 514/2

CLAIMS:

What is claimed is:

1. A method for treating a heterogeneous population of cancer cells in a living host by at least a first therapeutic agent and an additional therapeutic agent, the living host being a natural system composed of extra-cellular fluid and normal cells and cancer cells growing in the extra-cellular fluid, the normal cells containing soluble and cellular components which can attack and kill cancer cells, the normal cells growing in a normal extra-cellular matrix, the normal extra-cellular matrix having at least collagen and fibronectin, the heteragenous population of cancer cells growing in a cancer-altered extra-cellular matrix having at least cancer-altered antigenic epitopes, the heterogeneous population of cancer cells endogenously making and containing products selected from the group consisting of sulphated glycosaminoglycans, natural intra-cellular enzymes in the natural enzyme-rich vacuoles contained in the cell which are lysosomes, and natural intra-cellular material selected from the group consisting of DNA, histone and complexes of DNA-histone, the DNA, histone and complexes of DNA-histone having antigenic epitopes, the heterogeneous population of cancer cells selected from the group consisting of least three sub-populations of cancer cells:

a first sub-population of cancer cells being first target cancer cells each having a first antigenic receptor which is substantially specific to a cancer cell and which binds a first targeting agent, the first antigenic receptor inducing endocytosis when the first targeting agent binds to the first antigenic receptor;

the first target cancer cells having a sensitivity to being killed by the natural system of the living host and a sensitivity to being killed by the first therapeutic agent; and

a second sub-population of cancer cells being second target cancer cells each having a third antigenic receptor which is substantially specific to a cancer cell and which binds a third targeting agent, the third antigenic receptor being incapable of endocytosis; and

a third sub-population of cancer cells being non-target cancer cells which are the remainer of the cancer cells;

the normal cells of the living host endogenously making and containing products selected from the group consisting of sulphated glycosaminoglycans, natural intra-cellular enzymes in their lysosomes, and natural intra-cellular material selected from the group consisting of DNA, histone and complexes of DNA-histone, the DNA, histone and complexes of DNA-histone having antigenic epitopes, the normal cells selected from the group consisting of two sub-populations of normal cells:

a first sub-population of normal cells having first target normal cells which also have the first antigenic receptor and further having a sensitivity to being killed by the natural system of the living host and a sensitivity to being killed by the first therapeutic agent, the first target normal cells further having a second antigenic receptor which is substantially specific to normal cells and which binds a second targeting agent, the second antigenic receptor being induced to endocytose when the second targeting agent binds to the second antigenic receptor; and

the second sub-population of normal cells having non-target normal cells which are the remainder of the normal cells;

the method comprising the steps of:

administering to the living host a therapeutic effective amount of a soluble binary reagent including the first targeting agent which has substantial affinity for the first antigenic receptors, the binary reagent further including a soluble precipitable material which is attached to the first targeting agent;

allowing the soluble binary reagent to be endocytosed into the lysosomes of the first target cancer cells and into the lysosomes of the first target normal cells, the endocytosing and the natural intra-cellular enzymes in the lysosomes of the cells causing the soluble precipitable material to detach from the first targeting agent and thereby enabling the soluble precipitable material, upon being detached, to from a precipitate which has at least one of a first antigenic epitope being an epitope which is an integral part of the precipitate, a second antigenic epitope, and a neo-antigenic third epitope, the precipitate accumulating in the lysosomes within the first target cancer cells and within the first target normal cells;

continuing the administering of the soluble binary reagent into the

living host to increase the accumulation of the precipitate in the first target cancer cells and in the first target normal cells to form a quantity of antigenic epitopes which is proportional to the amount of accumulation of the precipitate;

administering to the living host a therapeutic effective amount of the first therapeutic agent which causes a cell-killing process which kills the first target cancer cells and the first target normal cells and thereby causing the accumulation of the precipitate having the quantity of antigenic epitopes to be relocated into the extra-cellular fluid adjacent to the first target cancer cells and to the first target normal cells, the relocated precipitate now becoming a first extra-cellular precipitate having the quantity of antigenic epitopes, the cell killing process further causing the relocation of the natural intra-cellular material having antigenic epitopes to the extra-cellular fluid adjacent to the first target cancer cells and the first target normal cells;

administering to the living host a therapeutic effective amount of a bispecific reagent including a non-mammalian enzyme moiety, the bispecific reagent further including a targeting agent moiety having substantial affinity for one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, the bispecific reagent being received and bound at the first extra-cellular precipitate, the first extra-cellular precipitate being retained in the extra-cellular fluid for a period of time, which enables the non-mammalian enzyme moiety to convert an amount of an additional therapeutic agent into a new form adapted to remain adjacent to the first extra-cellular precipitate for a period of time sufficient to kill non-selectively all cells adjacent to the first extra-cellular precipitate; and

administering to a living host a therapeutic effective amount of the additional therapeutic agent which is a soluble radioactive toxic agent to be converted by the non-mammalian enzyme moiety into a new form which remains adjacent to the first extra-cellular precipitate for a period of time sufficient to kill non-selectively all cells adjacent to the first extra-cellular precipitate.

2. A method in accordance with claim 1 in which the soluble precipitable material is an organic chemical comprising at least one member selected from the group consisting of opio-melanins, cellulose, chitosan, chitin, and indoxyl compounds having molecular positions of 1-7.

3. A method according to claim 1 in which the soluble precipitable material is radio-labeled.

4. A method in accordance with claim 1 in which the soluble precipitable material is converted by the natural intra-cellular enzymes into the intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

5. A method in accordance with claim 1 in which the soluble

precipitable material is a soluble material which when detached from the first targeting agent is converted by at least of the natural intra-cellular enzymes into an insoluble intra-cellular precipitate, the insoluble intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

6. A method in accordance with claim 1 in which the soluble precipitable material which is converted by at least one of the natural intra-cellular enzymes into an insoluble intra-cellular precipitate has a neo-antigenic third epitope the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate and having a neo-antigenic third epitope.

7. A method in accordance with claim 1 in which the soluble precipitable material is converted by at least one of the natural intra-cellular enzymes in the lysosomes into a soluble intermediate molecule, the soluble intermediate molecule being converted in the natural system of the host cells into the intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

8. A method in accordance with claim 1 in which the soluble precipitable material is converted by at least one of the natural intra-cellular enzymes in the lysosomes into a soluble intermediate molecule, the soluble intermediate molecule being oxidized by the natural environment in the host cell, thereby forming an oxidized soluble intermediate molecule, the oxidized soluble intermediate molecule spontaneously dimerizing and thereby making an insoluble molecule which forms the intra cellular precipitate which has a neo-antigenic third epitope not present on the soluble precipitable material from which the intra-cellular precipitate was formed, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate having a neo-antigenic third epitope.

9. A method in accordance with claim 2 in which the indoxyl compounds include at least one selected from the group consisting of sulphates, phosphates, glycosides, lipids, peptides, and nucleic acids which when attached to position 3 of the indoxyl compounds are cleavable by the natural intra-cellular enzymes in the lysosomes, the compound remaining after cleaving at position 3 being a soluble reactive intermediate molecule which is oxidized in the natural environment of the host cell thereby forming an oxidized soluble intermediate, the oxidized soluble intermediate spontaneously dimerizing and thereby forming an intra cellular precipitate which has a neo antigenic third epitope not present ran the indoxyl compounds from which the intra-cellular precipitate was formed, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate having a neo-antigenic third epitope.

10. A method in accordance with claim 2 in which each of the indoxyl compounds includes a substance which when attached to at least one of positions 4, 5, 6, and 7 of the indoxyl compound

alters the characteristics of the indoxyl compounds and the intra-cellular precipitate thereof, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

11. A method in accordance with claim 2 in which each of the indoxyl compounds includes phenyl compounds attached at position 5 of the indoxyl compound to alter the characteristics of the indoxyl compounds and the intra cellular precipitate thereof, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

12. A method in accordance with claim 2 in which each of the indoxyl compounds includes benzyloxy compounds attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and the intra-cellular precipitate thereof, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

13. A method in accordance with claim 2 in which each of the indoxyl compounds includes 5,5-bi-indoxyls attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and the intra-cellular precipitate thereof, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

14. A method in accordance with claim 1 in which the soluble precipitable material includes both a third and a fourth soluble chemicals, each of the third and fourth soluble chemicals being attached to the targeting agent, the third and fourth soluble chemicals when detached from the targeting agent, reacting with each other to form the intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

15. A method in accordance with claim 1 in which the soluble precipitate material is selected from the group consisting of a chemical including dicationic amphiphillic compounds including tilorone and acradine orange, the soluble precipitable material upon being detached from the first targeting agent reacting with the endogenously made products of the cancer cells and of the normal cells thereby forming a complex comprised of the soluble precipitable material and the endogenously made products, the complex precipitating inside the targeted cells and the intra-cellular precipitate so formed becoming relatively non-digestible, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

16. A method in accordance with claim 1 in which the soluble precipitable material is composed of a soluble moiety and insoluble moiety, the soluble precipitable material being converted by the natural intra cellular enzymes into an intra cellular precipitate, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

17. A method in accordance with claim 1 in which the soluble

precipitable material is composed of a soluble moiety and insoluble moiety, the soluble precipitable material being converted by the natural intra-cellular enzymes into an intra-cellular precipitate which has a neo-antigenic third epitope, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular preipitate having a neo-antigenic third epitope.

18. A method in accordance with claim 1 in which the soluble precipitable material has a soluble moiety and an insoluble moiety, the soluble moiety having a solubilizing effect on the insoluble moiety and being cleaved by the natural intra-cellular enzymes in the lysosomes from the insoluble moiety, the solubilizing effect or the soluble moiety being thereby dissipated and the remaining material, being insoluble, spontaneously forming an intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

19. A method in accordance with claim 1 in which the soluble precipitable material has a soluble moiety and an insoluble moiety, the soluble moiety having a solubilizing effect on the insoluble moiety, the soluble moiety being at least partially digested by the natural intra-cellular enzymes in the lysosomes, thereby dissipating the solubilizing effect or the soluble moiety, the insoluble moiety thereby spontaneously forming an intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra cellular fluid becoming the first extra cellular precipitate.

20. A method in accordance with claim 1 in which the soluble precipitable material has a soluble moiety and an insoluble moiety, the soluble moiety having a peptide moiety with a substantial binding affinity for the insoluble moiety and having a solubilizing effect on the insoluble moiety, the peptide moiety of the soluble moiety being partially digested by the natural intra-cellular enzymes in the lysosomes, the binding affinity of the peptide moiety having dissipated and thereby detaching the soluble moiety and eliminating the solubilizing effect of the soluble moiety, the remaining insoluble moiety spontaneously forming an intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate which later binds a peptide which has an affinity for the insoluble moiety.

21. A method in accordance with claim 1 in which the soluble precipitable material has a first chemical attached to reduce the rate of exit from the first target cancer cells and the first target normal cells of the soluble precipitable material prior to the soluble precipitable material forming an intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra cellular fluid becoming the first extra-cellular precipitate.

22. A method in accordance with claim 2 in which the indoxyl compounds have a first chemical attached to positions 4, 5, 6, and 7 of the indoxyl compounds to reduce substantially the rate of exit

from the cells of the soluble indoxyl compound prior to the soluble indoxyl compounds forming an intra-cellular precipitate, the intra-cellular precipitate when later relocated into the extra-cellular fluid becoming the first extra-cellular precipitate.

23. A method in accordance with claim 22 in which the first chemical is attached to the indoxyl compounds by a bond which is incapable of being cleaved by mammalian and non-mammalian enzymes.

24. A method in accordance with claim 1 in which the first antigenic epitope is a portion of the first extra-cellular precipitate and is a portion of the soluble precipitable material from which the first extra-cellular precipitate was formed.

25. A method in accordance with claim 1 in which a second chemical is attached to the soluble precipitable material, the second chemical having an antigenic epitope which is present as the second antigenic epitope on the first extra-cellular precipitate.

26. A method in accordance with claim 2 in which a second chemical is attached to the indoxyl compounds at positions 4, 5, 6, or 7, the second chemical having an antigenic epitope which is present as the second antigenic epitope on the first extra-cellular precipitate.

27. A method in accordance with claim 1 in which the second antigenic epitope on the first extra-cellular precipitate is cleaved by non-mammalian enzymes and incapable of being cleaved by mammalian enzymes and incapable of being cleaved by the non-mammalian enzyme moiety of the bispecific reagent attached to the first extra-cellular precipitate.

28. A method in accordance with claim 1 in which tile first extra-cellular precipitate is at least one of a non metabolizable precipitate and a precipitate metabolizable by at least one of mammalian enzymes and non-mammalian enzymes.

29. A method in accordance with claim 28 in which the first extra-cellular precipitate is metabolizable at a rate which is controlled by the properties of the precipitate.

30. A method in accordance with claim 1 in which the first extra-cellular precipitate has at least one of a non-ordered structure such as one of an agregate and an ordered structure such as one of a linear polymer.

31. A method in accordance with claim 1 in which the first extra-cellular precipitate is insoluble or slightly soluble in the extra-cellular fluid found in the living host.

32. A method in accordance with claim 1 and further comprising the step of additionally administering to the living host a second binary reagent prior to and during the time of the administering of the binary reagent, the second binary reagent including the second targeting agent having a substantially specific binding affinity for the second antigenic receptor, the binding thereby inducing endocytosis, the second binary reagent being attached to the second

targeting agent and, when detached, inhibiting the soluble precipitable material from forming an intra-cellular precipitate in the first target normal cells.

33. A method in accordance with claim 1 and further comprising the step of further administering to the living host a third binary reagent prior to and during the time of the administering of the first therapeutic agent, the third binary reagent including a second targeting agent having a substantially specific binding affinity for the second antigenic receptor, the binding thereby inducing endocytosis, the third binary reagent further including a material attached to the second targeting agent and, when detached, protecting the first target normal cells from being killed by the first therapeutic agent.

34. A method in accordance with claim 1 and further comprising the step of further administering a non-mammalian free enzyme to the living host prior to the step of administering the first therapeutic agent, the non mammalian free enzyme altering the precipitate formed in the extra-cellular fluid and resulting in antibodies and peptides which have an affinity for the precipitate to be unable to bind to the precipitate.

35. The method in accordance to claim 31 in which the altering of the precipitate comprising cleaving of the second antigenic epitope of the precipitate.

36. A method in accordance with claim 34 in which the altering of the precipitate comprising digesting of the precipitate.

37. A method in accordance with claim 34 and further comprising the step of still further administering to the living host an agent which causes the elimination of the free non-mammalian enzyme from the extra-cellular fluid.

38. A method in accordance with claim 34 and further comprising the step of still further administering to the living host an agent which inhibits the action of the free non-mammalian enzyme.

39. A method in accordance with claim 1 in which the administering of the first therapeutic agent for causing the cell killing process includes the administering of at least a cytotoxic agent which selectively kills the first target cancer cells.

40. A method in accordance with claim 1 in which the administering of the first therapuetic agent for causing the cell killing process includes the administering of at least a non cytotoxic agent which selectively kills the first target cancer cells.

41. A method in accordance with claim 1 in which the administering of the first therapeutic agent for causing the cell killing proces includes the administering of a procedure which alters hormonal status and which selectively kills the first target cancer cells.

42. A method in accordance with claim 1 in which the administering of the first therapeutic agent for causing the cell killing process includes a cell killing process which induces lysis and thereby

selectively kills the first target cancer cells.

43. A method in accordance with claim 1 in which the targeting agent moiety of the bispecific reagent has a substantial affinity for the first antigenic epitope of the first extra-cellular precipitate.

44. A method in accordance with claim 1 in which the targeting agent moiety of the bispecific reagent has a substantial affinity for the second antigenic epitope of the first extra-cellular precipitate.

45. A method in accordance to claim 1 in which the targeting agent moiety of the bispecific reagent has a substantial affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

46. A method in accordance with claim 1 in which the non-mammalian enzyme moiety of the bispecific reagent is beta lactamase.

47. A method in accordance with claim 1 in which the non-mammalian enzyme moiety of the bispecific reagent is a penicillinase.

48. A method in accordance with claim 1 in which the non-mammalian enzyme moiety of the bispecific reagent is a glycosidase.

49. A method in accordance with claim 1 in which the non-mammalian enzyme moiety of the bispecific reagent is chondroitinase ABC.

50. A method in accordance with claim 1 in which the additional therapeutic agent is a soluble radioactive toxic agent and is an organic chemical selected from the group consisting of opio-melanins, cellulose, chitosan, chitin, proteoglycans, synthetic polymers, and indoxyl compounds having molecular positions 1-7.

51. A method in accordance with claim 1 in which the additional therapeutic agent is cell impermeant.

52. A method in accordance with claim 1 in which a cell-impermeant chemical is attached to the additional therapeutic agent the cell-impermeant chemical causing the additional therapeutic agent to become cell impermeant.

53. A method in accordance with claim 52 in which the cell-impermeant chemical is selected from the group consisting of thiol, anionic materials, and materials having a molecular weight greater than 1000 daltons.

54. A method in accordance with claim 1 in which the additional therapeutic agent is a second therapeutic agent, the second therapeutic agent being a soluble molecule which is converted by the non-mammalian enzyme moiety of the bispecific reagent into a new form which is insoluble and forms the second extra-cellular precipitate.

55. A method in accordance with claim 1 in which the additional

therapeutic agent is a second therapeutic agent, the second therapeutic agent being a soluble molecule which is converted by the non-mammalian enzyme moiety of the bispecific reagent into a new form which is insoluble the new form being a second extra-cellular precipitate, the second extra-cellular precipitate having a neo-antigenic epitope not present on the second therapeutic agent from which the second extra-cellular precipitate was formed.

56. A method in accordance with claim 1 in which the additional therapeutic agent is a second therapeutic agent, the second therapeutic agent being converted by the non mammalian enzyme moiety of the bispecific reagent into a soluble intermediate molecule, the soluble intermediate molecule being naturally converted in the extra-cellular fluid into a new form which is insoluble, the new form being the second extra-cellular precipitate.

57. A method in accordance with claim 1 in which the additional therapeutic agent is a second therapeutic agent, the second therapeutic agent being oxidized and thereby forming an oxidized soluble intermediate molecule,

the oxidized soluble intermediate molecule spontaneously being dimerized and thereby making a new form which is insoluble, the new form being the second extra-cellular precipitate, the second extra-cellular precipitate having a neo-antigenic epitope not present on the second therapeutic agent from which it was formed.

58. A method in accordance with claim 50 in which the indoxyl compounds are selected from the group consisting of indoxyl-penicillin, indoxyl-cephalosporin, and indoxyl-glycosides which when attached to position 3 of the indoxyl compounds bar cleavable by the non-mammalian enzyme moiety of the bispecific reagent, the compound remaining after cleaving at position 3 being a soluble reactive intermediate molecule which oxidizes and dimerizes to make a new form which is insoluble, the new form being the second extra-cellular precipitate.

59. A method in accordance with claim 50 in which each of the indoxyl compounds includes a substance when attached to at least one of positions 4, 5, 6, and 7 of the indoxyl compound alters the characteristics of the indoxyl compounds and the second extra-cellular precipitate.

60. A method in accordance with claim 50 in which each of the indoxyl compounds includes phenyl compounds attached at position 5 of the indoxyl compound to alter the characteristics of the indoxyl compounds and the second extra-cellular precipitate.

61. A method in accordance with claim 50 in which each of the indoxyl compounds is selected from benzyloxy compounds and attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and of the second extra-cellular precipitate.

62. A method in accordance with claim 50 in which each of the

indoxyl compounds includes 5,5-bi-indoxyls attached at position 5 of the indoxyl compounds to alter the characteristics of the indoxyl compounds and of the second extra-cellular precipitate.

63. A method in accordance with claim 1 in which the additional therapeutic agent is a second therapeutic agent, the second therapeutic agent having a soluble moiety and an insoluble moiety, the soluble moiety having a solubilizing effect on the insoluble moiety and being cleaved by the non-mammalian enzyme moiety of the bispecific reagent from the insoluble moiety, the solubilizing effect of the soluble moiety being thereby dissipated and the remaining moiety having been converted into a new form and being insoluble, spontaneously precipitates, and forms the second extra-cellular precipitate.

64. A method in accordance with claim 1 in which the additional therapeutic agent is a third therapeutic agent, the third therapeutic agent being converted by the non-mammalian enzyme moiety of the bispecific reagent into a new form, the new form being a soluble material having a neo-antigenic epitope not present on the third threapeutic agent from which the new form was created.

65. A method in accordance with claim 64 in which the third therapeutic agent is chondroitin sulphate which is converted by the non-mammalian enzyme moiety of the bispecific reagent into a new form, the new form of the third therapeutic agent being a soluble material with a neo-antigenic epitope not present on the chondroitin sulphate from which the new form of the third therapeutic agent was created.

66. The method in accordance with claim 64 and further comprising the step of administering to the living host a precipitating antibody having a specific affinity for the neo antigenic epitope on the new form of the third therapeutic agent the precipitating antibody being administered prior to the step of administering the third therapeutic agent and having the ability to bind to the neo-antigenic epitope of the new form of the third therapeutic agent, the binding causing the new form of the third theapeutic agent to form a third extra-cellular precipitate which remains for a period of time adjacent to the relocated first extra cellular precipitate.

67. A method according to claim 1 and further comprising the step of administering to the living host a second bispecific reagent to tether the first extra-cellular precipitate, the second bispecific reagent having two moieties, a first moiety having an affinity for one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, a second moiety having an affinity for the third antigenic receptor on the second target cancer cells, the second bispecific reagent being administered prior to the administration of the first therapeutic agent and enabling the fist extra-cellular precipitate to be retained for a period of time adjacent to the third antigenic receptor on the second target cancer cells.

68. A method according to 67 in which the first moiety of the second bispecific reagent has an affinity for the first antigenic

epitope of the first extra-cellular precipitate.

69. A method according to 67 in which the first moiety of the second bispecific reagent has an affinity for the second antigenic epitope of the first extra-cellular precipitate.

70. A method according to 67 in which the first moiety of the second bispecific reagent has an affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

71. A method according to claim 1 and further comprising the step of administering to the living host a third bispecific reagent, the third bispecific reagent having two moieties, a first moiety having an affinity for one of the first antigenic epitope, a second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, the second moiety having an affinity for the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix, the third bispecific reagent being administered prior to the administration of the first therapeutic agent and enabling the first extra-cellular precipitate to be retained for a period of time adjacent to the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix.

72. A method according to 71 in which the first moiety of the third bispecific reagent has an affinity for the first antigenic epitope of the first extra-cellular precipitate.

73. A method according to 71 in which the first moiety of the third bispecific reagent has an affinity for the second antigenic epitope of the first extra-cellular precipitate.

74. A method according to 71 in which the first moiety of the third bispecific reagent has an affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

75. A method according to claim 1 and further comprising the step of administering to the living host a fourth bispecific reagent, the fourth bispecific reagent having two moieties, a first moiety having an affinity for one of the first antigenic epitope, the second antigenic epitope, and the neo-antigenic third epitope of the first extra-cellular precipitate, a second moiety having an affinity for the antigenic epitopes on the relocated natural intra-cellular material, the fourth bispecifc reagent being administered prior to the administration of the first therapeutic agent and enabling the first extra-cellular precipitate to be retained for a period of time adjacent to the antigenic epitopes on the relocated natural intra-cellular material.

76. A method according to 75 in which the first moiety of the fourth bispecific reagent has an affinity for the first antigenic epitope of the first extra-cellular precipitate.

77. A method according to 75 in which the first moiety of the fourth bispecific reagent has an affinity for the second antigenic epitope of the first extra-cellular precipitate.

78. A method according to 75 in which the first moiety of the

fourth bispecific reagent has an affinity for the neo-antigenic third epitope of the first extra-cellular precipitate.

79. A method according to claim 55 and further comprising the stop of administering to the living host a fifth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope of the second extra-cellular precipitate, the fifth bispecific reagent further having a molecule with a substantial affinity for the third antigenic receptor on the second target cancer cell, the fifth bispecific reagent being administered prior to the step of additionally administering the second therapeutic agent and enabling the second extra-cellular precipitate to be retained for a period of time adjacent to the third antigenic receptor on the second target cancer cells.

80. A method according to claim 55 and further comprising the step of administering to the living host a sixth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope on the second extra-cellular precipitate, the sixth bispecific reagent further having a molecule with a substantial affinity for the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix, the sixth bispecific reagent being administered prior to the step of additionally administering the second therapeutic agent and enabling the second extra-cellular precipitate to be retained for a period of time adjacent to cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix.

81. A method according to claim 55 and further comprising the step of administering to the living host a seventh bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope on the second extra-cellular precipitate, the seventh bispecific reagent further having a molecule with a substantial affinity for the antigenic epitopes on the natural intra-cellular material, the seventh bispecific reagent being administered prior to the step of administering the second therapeutic agent and enabling the second extra-cellular precipitate to be retained for a period of time adjacent to the antigenic epitopes on the natural intra-cellular material.

82. A method according to claim 64 and further comprising the step of administering to the living host an eighth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope of the new form of the third therapeutic agent, the eighth bispecific reagent further having a molecule with a substantial affinity for the third antigenic receptor on the second target cancer cells, the eighth bispecific reagent to be administered prior to the step of administering the third therapeutic agent and enabling the new form of the third therapeutic agent to be retained for a period of time adjacent to the third antigenic receptor on the second target cancer cells.

83. A method according to claim 64 and further comprising the step of administering to the living host a ninth bispecific reagent comprised of a molecule having a substantial affinity for the neo antigenic epitope on the new form of the third therapeutic agent, the ninth bispecific reagent further having a molecule with a

substantial affinity for the cancer-altered antigenic epitopes on the cancer-altered extra-cellular matrix, the ninth bispecifc reagent being administered prior to the step of administering the third therapeutic agent and enabling the new form of the third therapeutic agent to be retained for a period of time adjacent to the cancer altered antigenic epitopes on the cancer-altered extra-cellular matrix.

84. A method according to claim 64 and further comprising the step of administering to the living host a tenth bispecific reagent comprised of a molecule having a substantial affinity for the neo-antigenic epitope on the new form of the third therapeutic agent, the tenth bispecific reagent further having a molecule with a substantial affinity for the antigenic epitopes on the natural intra-cellular material, the tenth bispecific reagent being administered prior to the step of administering the third therapeutic agent and enabling the new form of the third therapeutic agent to be retained for a period of time adjacent to the antigenic epitopes on the natural intra-cellular material.

85. A method in accordance with claim 13 in which two indoxyl compounds are attached via a spacer molecule.

86. A method in accordance with claim 62 in which two indoxyl compounds are attached via a spacer molecule.

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(57) Abstract

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunologically-based reagents. In particular aspects, antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens, or through the specific induction of endothelial cell surface antigens on vascular endothelial cells in solid tumors.

lymphoid antigens because the normal lymphocytes which ar killed along with the malignant cells during therapy are rapidly regenerated from progenitors lacking the target antigens. In Phase I trials where patients had large bulky tumor masses, greater than 50% tumor regressions were achieved in approximately 40% of the patients (Vitetta *et al.*, 1991). It is predicted that the efficacy of these immunotoxins in patients with less bulky disease will be even better.

In contrast with their efficacy in lymphomas, immunotoxins have proved relatively ineffective in the treatment of solid tumors such as carcinomas (Weiner *et al.*, 1989; Byers *et al.*, 1989). The principal reason for this is that solid tumors are generally impermeable to antibody-sized molecules: specific uptake values of less than 0.001% of the injected dose/g of tumor are not uncommon in human studies (Sands *et al.*, 1988; Epenetos *et al.*, 1986). Furthermore, antibodies that enter the tumor mass do not distribute evenly for several reasons. Firstly, the dense packing of tumor cells and fibrous tumor stromas present a formidable physical barrier to macromolecular transport and, combined with the absence of lymphatic drainage, create an elevated interstitial pressure in the tumor core which reduces extravasation and fluid convection (Baxter *et al.*, 1991; Jain, 1990). Secondly, the distribution of blood vessels in most tumors is disorganized and heterogeneous, so some tumor cells are separated from extravasating antibody by large diffusion distances (Jain, 1990). Thirdly, all of the antibody entering the tumor may become adsorbed in perivascular regions by the first tumor cells encountered, leaving none to reach tumor cells at more distant sites (Baxter *et al.*, 1991; Kennel *et al.*, 1991). Finally, antigen-deficient mutants can escape being killed by the immunotoxin and regrow (Thorpe *et al.*, 1988).